1249217

# THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

*November 15, 2004*

**THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.**

**APPLICATION NUMBER:** *60/507,810*
**FILING DATE:** *October 01, 2003*
**RELATED PCT APPLICATION NUMBER:** *PCT/US04/33058*

Certified by

Jon W Dudas

Acting Under Secretary of Commerce
for Intellectual Property
and Acting Director of the U.S.
Patent and Trademark Office

PTO/SB/17 (01-03)
Approved for use through 04/30/2003. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

# FEE TRANSMITTAL for FY 2003

*Effective 01/01/2003. Patent fees are subject to annual revision.*

☐ Applicant claims small entity status. See 37 CFR 1.27

**TOTAL AMOUNT OF PAYMENT** ($) 160.00

| Complete If Known | |
|---|---|
| Application Number | |
| Filing Date | Herewith |
| First Named Inventor | Rao et al |
| Examiner Name | |
| Art Unit | |
| Attorney Docket No. | AM-101457USA |

## METHOD OF PAYMENT *(check all that apply)*

☑ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☑ Deposit Account:

Deposit Account Number: HOWSON AND HOWSON

Deposit Account Name: 08-3040

The Commissioner is authorized to: *(check all that apply)*

☑ Charge fee(s) indicated below ☑ Credit any overpayments

☑ Charge any additional fee(s) during the pendency of this application

☑ Charge fee(s) indicated below, except for the filing fee to the above-identified deposit account.

## FEE CALCULATION

### 1. BASIC FILING FEE

| Large Entity Fee Code | Large Entity Fee ($) | Small Entity Fee Code | Small Entity Fee ($) | Fee Description | Fee Paid |
|---|---|---|---|---|---|
| 1001 | 750 | 2001 | 375 | Utility filing fee | |
| 1002 | 330 | 2002 | 165 | Design filing fee | |
| 1003 | 520 | 2003 | 260 | Plant filing fee | |
| 1004 | 750 | 2004 | 375 | Reissue filing fee | |
| 1005 | 160 | 2005 | 80 | Provisional filing fee | 160.00 |

SUBTOTAL (1) ($) 160.00

### 2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

| | Extra Claims | | Fee from below | | Fee Paid |
|---|---|---|---|---|---|
| Total Claims | | -20** = | | X | = |
| Independent Claims | | - 3** = | | X | = |
| Multiple Dependent | | | | | = |

| Large Entity Fee Code | Large Entity Fee ($) | Small Entity Fee Code | Small Entity Fee ($) | Fee Description |
|---|---|---|---|---|
| 1202 | 18 | 2202 | 9 | Claims in excess of 20 |
| 1201 | 84 | 2201 | 42 | Independent claims in excess of 3 |
| 1203 | 280 | 2203 | 140 | Multiple dependent claim, if not paid |
| 1204 | 84 | 2204 | 42 | ** Reissue Independent claims over original patent |
| 1205 | 18 | 2205 | 9 | ** Reissue claims in excess of 20 and over original patent |

SUBTOTAL (2) ($)

**or number previously paid, if greater; For Reissues, see above

## FEE CALCULATION (continued)

### 3. ADDITIONAL FEES

| Large Entity Fee Code | Large Entity Fee ($) | Small Entity Fee Code | Small Entity Fee ($) | Fee Description | Fee Paid |
|---|---|---|---|---|---|
| 1051 | 130 | 2051 | 65 | Surcharge - late filing fee or oath | |
| 1052 | 50 | 2052 | 25 | Surcharge - late provisional filing fee or cover sheet | |
| 1053 | 130 | 1053 | 130 | Non-English specification | |
| 1812 | 2,520 | 1812 | 2,520 | For filing a request for *ex parte* reexamination | |
| 1804 | 920* | 1804 | 920* | Requesting publication of SIR prior to Examiner action | |
| 1805 | 1,840* | 1805 | 1,840* | Requesting publication of SIR after Examiner action | |
| 1251 | 110 | 2251 | 55 | Extension for reply within first month | |
| 1252 | 410 | 2252 | 205 | Extension for reply within second month | |
| 1253 | 930 | 2253 | 465 | Extension for reply within third month | |
| 1254 | 1,450 | 2254 | 725 | Extension for reply within fourth month | |
| 1255 | 1,970 | 2255 | 985 | Extension for reply within fifth month | |
| 1401 | 320 | 2401 | 160 | Notice of Appeal | |
| 1402 | 320 | 2402 | 160 | Filing a brief in support of an appeal | |
| 1403 | 280 | 2403 | 140 | Request for oral hearing | |
| 1451 | 1,510 | 1451 | 1,510 | Petition to institute a public use proceeding | |
| 1452 | 110 | 2452 | 55 | Petition to revive - unavoidable | |
| 1453 | 1,300 | 2453 | 650 | Petition to revive - unintentional | |
| 1501 | 1,300 | 2501 | 650 | Utility issue fee (or reissue) | |
| 1502 | 470 | 2502 | 235 | Design issue fee | |
| 1503 | 630 | 2503 | 315 | Plant issue fee | |
| 1460 | 130 | 1460 | 130 | Petitions to the Commissioner | |
| 1807 | 50 | 1807 | 50 | Processing fee under 37 CFR 1.17(q) | |
| 1806 | 180 | 1806 | 180 | Submission of Information Disclosure Stmt | |
| 8021 | 40 | 8021 | 40 | Recording each patent assignment per property (times number of properties) | |
| 1809 | 750 | 2809 | 375 | Filing a submission after final rejection (37 CFR 1.129(a)) | |
| 1810 | 750 | 2810 | 375 | For each additional invention to be examined (37 CFR 1.129(b)) | |
| 1801 | 750 | 2801 | 375 | Request for Continued Examination (RCE) | |
| 1802 | 900 | 1802 | 900 | Request for expedited examination of a design application | |

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid SUBTOTAL (3) ($)

(Complete *if applicable*)

| SUBMITTED BY | | | | | |
|---|---|---|---|---|---|
| Name (Print/Type) | Cathy A. Kodroff | Registration No. (Attorney/Agent) | 33,980 | Telephone | 215-540-9200 |
| Signature | Cathy A Kodroff | | | Date | October 1, 2003 |

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

This collection of information is required by 37 CFR 1.17 and 1.27. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: **Commissioner for Patents, Washington, DC 20231.**

*If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.*

Express Mail No. EU 531574100US Customer No. 38199

PTO/SB/17 (01-03)
Approved for use through 04/30/2003. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

# FEE TRANSMITTAL for FY 2003

*Effective 01/01/2003. Patent fees are subject to annual revision.*

☐ Applicant claims small entity status. See 37 CFR 1.27

**TOTAL AMOUNT OF PAYMENT** ($) 160.00

| *Complete If Known* | |
|---|---|
| Application Number | |
| Filing Date | Herewith |
| First Named Inventor | Rao et al |
| Examiner Name | |
| Art Unit | |
| Attorney Docket No. | AM-101457USA |

## METHOD OF PAYMENT *(check all that apply)*

☑ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☑ Deposit Account:

Deposit Account Number: HOWSON AND HOWSON

Deposit Account Name: 08-3040

The Commissioner is authorized to: *(check all that apply)*

☑ Charge fee(s) indicated below ☑ Credit any overpayments

☑ Charge any additional fee(s) during the pendency of this application

☑ Charge fee(s) indicated below, **except for the filing fee** to the above-identified deposit account.

## FEE CALCULATION

### 1. BASIC FILING FEE

| Large Entity Fee Code | Large Entity Fee ($) | Small Entity Fee Code | Small Entity Fee ($) | Fee Description | Fee Paid |
|---|---|---|---|---|---|
| 1001 | 750 | 2001 | 375 | Utility filing fee | |
| 1002 | 330 | 2002 | 165 | Design filing fee | |
| 1003 | 520 | 2003 | 260 | Plant filing fee | |
| 1004 | 750 | 2004 | 375 | Reissue filing fee | |
| 1005 | 160 | 2005 | 80 | Provisional filing fee | 160.00 |

SUBTOTAL (1) ($) 160.00

### 2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

| | Extra Claims | | Fee from below | | Fee Paid |
|---|---|---|---|---|---|
| Total Claims | | -20** = | | X | = |
| Independent Claims | | - 3** = | | X | = |
| Multiple Dependent | | | | | = |

| Large Entity Fee Code | Large Entity Fee ($) | Small Entity Fee Code | Small Entity Fee ($) | Fee Description |
|---|---|---|---|---|
| 1202 | 18 | 2202 | 9 | Claims in excess of 20 |
| 1201 | 84 | 2201 | 42 | Independent claims in excess of 3 |
| 1203 | 280 | 2203 | 140 | Multiple dependent claim, if not paid |
| 1204 | 84 | 2204 | 42 | ** Reissue independent claims over original patent |
| 1205 | 18 | 2205 | 9 | ** Reissue claims in excess of 20 and over original patent |

SUBTOTAL (2) ($)

**or number previously paid, if greater; For Reissues, see above

## FEE CALCULATION (continued)

### 3. ADDITIONAL FEES

| Large Entity Fee Code | Large Entity Fee ($) | Small Entity Fee Code | Small Entity Fee ($) | Fee Description | Fee Paid |
|---|---|---|---|---|---|
| 1051 | 130 | 2051 | 65 | Surcharge - late filing fee or oath | |
| 1052 | 50 | 2052 | 25 | Surcharge - late provisional filing fee or cover sheet | |
| 1053 | 130 | 1053 | 130 | Non-English specification | |
| 1812 | 2,520 | 1812 | 2,520 | For filing a request for *ex parte* reexamination | |
| 1804 | 920* | 1804 | 920* | Requesting publication of SIR prior to Examiner action | |
| 1805 | 1,840* | 1805 | 1,840* | Requesting publication of SIR after Examiner action | |
| 1251 | 110 | 2251 | 55 | Extension for reply within first month | |
| 1252 | 410 | 2252 | 205 | Extension for reply within second month | |
| 1253 | 930 | 2253 | 465 | Extension for reply within third month | |
| 1254 | 1,450 | 2254 | 725 | Extension for reply within fourth month | |
| 1255 | 1,970 | 2255 | 985 | Extension for reply within fifth month | |
| 1401 | 320 | 2401 | 160 | Notice of Appeal | |
| 1402 | 320 | 2402 | 160 | Filing a brief in support of an appeal | |
| 1403 | 280 | 2403 | 140 | Request for oral hearing | |
| 1451 | 1,510 | 1451 | 1,510 | Petition to institute a public use proceeding | |
| 1452 | 110 | 2452 | 55 | Petition to revive - unavoidable | |
| 1453 | 1,300 | 2453 | 650 | Petition to revive - unintentional | |
| 1501 | 1,300 | 2501 | 650 | Utility issue fee (or reissue) | |
| 1502 | 470 | 2502 | 235 | Design issue fee | |
| 1503 | 630 | 2503 | 315 | Plant issue fee | |
| 1460 | 130 | 1460 | 130 | Petitions to the Commissioner | |
| 1807 | 50 | 1807 | 50 | Processing fee under 37 CFR 1.17(q) | |
| 1806 | 180 | 1806 | 180 | Submission of Information Disclosure Stmt | |
| 8021 | 40 | 8021 | 40 | Recording each patent assignment per property (times number of properties) | |
| 1809 | 750 | 2809 | 375 | Filing a submission after final rejection (37 CFR 1.129(a)) | |
| 1810 | 750 | 2810 | 375 | For each additional invention to be examined (37 CFR 1.129(b)) | |
| 1801 | 750 | 2801 | 375 | Request for Continued Examination (RCE) | |
| 1802 | 900 | 1802 | 900 | Request for expedited examination of a design application | |

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid SUBTOTAL (3) ($)

| SUBMITTED BY | | | | (Complete *if applicable*) | |
|---|---|---|---|---|---|
| *Name (Print/Type)* | Cathy A. Kodroff | *Registration No. (Attorney/Agent)* | 33,980 | *Telephone* | 215-540-9200 |
| *Signature* | Cathy A Kodroff | | | *Date* | October 1, 2003 |

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

This collection of information is required by 37 CFR 1.17 and 1.27. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, Washington, DC 20231.**

*If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.*

Express Mail No. EU 531574100US Customer No. 38199

PTO/SB/16 (10-01)
Approved for use through10/31/2002. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

# PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

| Express Mail Label No. | EU531574100US |
|---|---|

**INVENTOR(S)**

| Given Name (first and middle [if any]) | Family Name or Surname | Residence (City and either State or Foreign Country) |
|---|---|---|
| Sripriya | Venkata Ramana Rao | New City, NY |

☑ *Additional inventors are being named on the* 1 *separately numbered sheets attached hereto*

**TITLE OF THE INVENTION (500 characters max)**

Pantoprazole Microparticulate Formulations

*Direct all correspondence to:* **CORRESPONDENCE ADDRESS**

☐ Customer Number 38199 → *Type Customer Number here*

OR

*Place Customer Number Bar Code Label here*

| | | | | | |
|---|---|---|---|---|---|
| ☐ Firm or Individual Name | HOWSON AND HOWSON | | | | |
| Address | Spring House Corporate Center | | | | |
| Address | 321 Norristown Road, Box 457 | | | | |
| City | Spring House | State | PA | ZIP | 19477 |
| Country | USA | Telephone | 215-540-9200 | Fax | 215-540-5818 |

**ENCLOSED APPLICATION PARTS** *(check all that apply)*

☑ Specification *Number of Pages* 14
☐ Drawing(s) *Number of Sheets*
☐ Application Data Sheet. See 37 CFR 1.76
☐ CD(s), Number
☐ Other (specify)

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ Applicant claims small entity status. See 37 CFR 1.27.
☑ A check or money order is enclosed to cover the filing fees
☑ The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 08-3040
☐ Payment by credit card. Form PTO-2038 is attached.

FILING FEE AMOUNT ($): $160.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☑ No.
☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

*Respectfully submitted,*

SIGNATURE Cathy A. Kodroff

TYPED or PRINTED NAME Cathy A. Kodroff

TELEPHONE 215-540-9200

Date 10/01/2003

REGISTRATION NO. *(if appropriate)* 33,980

Docket Number: AM-101457USA

## USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C. 20231.

Customer No. 38,199

# *PROVISIONAL APPLICATION COVER SHEET*
*Additional Page*

PTO/SB/16 (02-01)
Approved for use through 10/31/2002. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE


| Docket Number | AM-101457USA |
|---|---|

**INVENTOR(S)/APPLICANT(S)**

| Given Name (first and middle [if any]) | Family or Surname | Residence (City and either State or Foreign Country) |
|---|---|---|
| Syed M. | Shah | East Hanover, NJ |
| Hanumantharao | Tatapudy | Suffern, NY |
| Richard William | Saunders | Palisades, NY |
| Mahdi | Fawzi | Morristown, NJ |

Number 1 of 1

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

AM-101457

# PANTOPRAZOLE MICROPARTICULATE FORMULATIONS

## BACKGROUND OF THE INVENTION

Pantoprazole, 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl)methylsulphinyl]-1H-benzimidazole, is a H+/K+-ATPase inhibitor.

The current commercial oral formulations of sodium pantoprazole are single unit coated tablets. See, e.g., US Patent 5997903, which describes oral forms of pantoprazole that consist of a core, an intermediate layer and an outer layer.

Multiparticulate formulations, because of their nature of dispersing in the gastrointestinal tract, show a reduced food effect and variability in gastric emptying times, thereby providing for reduced inter and intra subject variability, as compared to single unit tablets (Intl. Journal of Pharmaceutics 140 [1996] 229-235).

The current coating has a tendency to cause undesirable sticking of the tablet to the gastrointestinal tract. Several unsuccessful attempts have been made in the past to develop a stable formulation of pantoprazole that avoids this effect.

## SUMMARY OF THE INVENTION

The invention provides a stable multiparticulate formulation of sodium pantoprazole that provides reduced inter and intra subject variability. This formulation is less prone to adherence to the intestinal walls, nasogastric and gastromy tubes, thereby giving predictable delivery of the drug product to the site of drug release. It also provides for an early onset of action for relief of gastro-intestinal pain and has a prolonged duration of action. This formulation allows dosing to pediatric patients and patients who have difficulty swallowing solid foods. This formulation also allows for drug delivery via nasogastric and gastrostomy tubes.

## DETAILED DESCRIPTION OF THE INVENTION

In one aspect, the invention provides multiparticulate formulations of pantoprazole having reduced release under gastric conditions and fast release at neutral pH, *i.e.*, in the lower gastrointestinal tract.

The multi particulate formulation of sodium pantoprazole of the invention provides an enhanced system for the delivery of pantoprazole to patients. The current marketed formulation is a single monolithic tablet. The present formulation of multiparticulate spheroids, which is adaptable for use in a capsule or a foil packet, is prepared by extrusion/spheronization plus coating technology.

The composition of the multiparticle of the invention, and the Eudragit enteric coat allows for reduced release at low pH (~ 1) and fast release at a neutral pH (~7). This provides faster blood levels of the drug, in patients, and thereby a faster onset of action. The smaller $T_{lag}$ value of multiparticulate formulation as compared to that of a single monolithic tablet based on the results from dog data indicates faster onset of action of multiparticulate formulation.

The use of a multi particulate formulation facilitates dosing to pediatric patients and patients who have trouble swallowing, by dispersing the spheroids in a suspending liquid or sprinkling /dispersing in a low pH liquid like applesauce, prior to administration. The smaller size of the multi particulates, in a capsule or pouch or any other container, also allows dosing through nasogastric or gastrostomy tube.

This formulation allows for a faster relief of GI pain and prolonged duration of action (extended release), as compared to the current marketed tablet.

### I. Multiparticulates of the Invention

Typically, the multiparticles of the invention are no greater than about 1mm in size in order to facilitate passage through nasogastric tubes. Suitably, the multiparticles are in the range of about 0.1 to 1 mm, or 0.5 mm to 1 mm, or 0.7 mm to 0.9 mm.

The multiparticles of the invention are composed, at a minimum, of a spheroid core with an enteric coat over the core. The spheroid core is composed of, at a minimum, a pantoprazole or a salt thereof, and a surfactant.

As used herein, the term pantoprazole refers to 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl)methylsulphinyl]-1H-benzimidazole and enantiomers thereof. The active compound, pantoprazole is described in European Patent 166 287, which describes the preparation thereof. Examples of suitable salts of pantoprazole include, e.g., sodium magnesium, and calcium, among others; still others are described in the European Patent 166 286, which is incorporated by reference herein. The selection of a suitable salt is not a limitation of the invention. In one embodiment, the salt is sodium. Typically, the pantoprazole compound is present in the range of from about 5 to 50 % w/w, more preferably about 20 to 45 % w/w, of the spheroid core.

Suitable surfactants are known to those of skill in the art. However, particularly desirable are polysorbates, including, e.g., polysorbate 80. Typically, the surfactant is present in the core in an amount of about 2 to about 7 % w/w, and desirably, about 5% w/w of the core. Advantageously, the polysorbates, in the multiparticulate formulation have been found to enhance the speed and extent of release and absorption of the sodium pantoprazole, from the multi particulate formulation of the invention.

The spheroid core can further contain a binder, a pH adjuster and hypromellose. Suitably, the total amount of binder(s) present in the core is an amount of about 15 % w/w to about 80 % w/w, or about 20% w/w to about 70 % w/w, or about 25% w/w to about 45% w/w, or about 30% w/w to about 42 % w/w. The total amount of a pH adjuster in the formulation can range from about 0.1% w/w to about 10% w/w of the core, or about 1% w/w to about 8% w/w, or about 3% w/w to about 7% w/w. However, these percentages can be adjusted as needed or desired by one of skill in the art.

The binder may be selected from among known binders, including, e.g., cellulose, and povidone, among others. In one embodiment, the binder is selected from among microcrystalline cellulose and crospovidone, and mixtures thereof. Suitable pH adjusters include, e.g., sodium carbonate, sodium bicarbonate, potassium carbonate, lithium carbonate, among others. Still other suitable components will be readily apparent to one of skill in the art.

In one embodiment, the spheroid core contains:

| | |
|---|---|
| pantoprazole sodium sesquihydrate | 45.24% w/w |
| microcrystalline cellulose | 27.25% w/w |

| | | |
|---|---|---|
| polysorbate 80 | 5 % | w/w |
| crospovidone | 15 % | w/w |
| hypromellose 2208 | 1 % | w/w |
| sodium carbonate | 6.5% | w/w |
| purified water | q.s. | |

Optionally, an initial seal coat can be applied directly to the core prior to coating with the enteric coat. Although the components of this seal coat can be modified by one of skill in the art, a particularly suitable initial seal coat is composed of hydroxypropyl methylcellulose (HPMC) and water. For example, a suitable initial seal coat can be applied as a 7.5% w/w HPMC solution. Typically, such a seal coat is in the range of about 1 % w/w to about 3% w/w of the resulting coated multiparticulate.

The enteric coat is applied over the initial seal coat, if present, or directly to the uncoated spheroid core. Suitably, the enteric coat is applied such that it coats the microparticulate in an amount of about 15 to 45 % w/w, or about 20 % w/w to about 30% w/w, or about 25% w/w to 30% w/w of the microparticle. In one embodiment, the enteric coat is about 27.5 to 32. 5 % w/w of the microparticulate. Suitably, the enteric coat contains a product which is a copolymer of methacrylic acid and methacrylates, such as the commercially available Eudragit L 30 K55. In one embodiment, the enteric coat is composed of a Eudragit L30D-55 copolymer, talc, trimethyl citrate, and water. More particularly, the enteric coating may contain about 30% w/w of a 30 wt% dispersion of Eudragit L 30 D55 coating; about 15% w/w talc, about 3% triethyl citrate; a pH adjuster such as sodium hydroxide and water.

In one embodiment, the enteric-coated microparticulate is further coated with a final seal coat. Suitably, this final seal coat is composed of HPMC and water, and is less than about 1 wt% of the microparticle.

Without wishing to be bound by theory, it is believed that HPMC provides a physical barrier for reduced contact between the mucoadhesive Eudragit layer and the upper GI tract, and thereby allows the reliable transit of the multi particulates to the proper pH environment in the GI tract for effective release and absorption of the drug.

Suitably, when prepared as described herein, the microparticulates of the invention have an average size no greater than about 1mm in diameter, and preferably are in the range of about 0.1 mm to about 1 mm. However, larger microparticulates may be prepared if desired for specific indications.

## II. Method of Producing Multiparticulate Formulations of Invention

In another aspect, the invention provides a method of producing the multiparticulate formulations of the invention.

Typically, the uncoated pantoprazole compounds are prepared are follows. The dry components, including, at least the pantoprazole compound and the binder are dry blended in a suitable mixer, e.g., a Hobart mixer. Optionally, the HPMC and a pH adjuster may be included in this step. Subsequently, the liquid components, e.g., the surfactant and water, are mixed in to afford a granulated product. The granulation is then extruded and spheronized through a suitable device (e.g., a Nica extruder/spheronizer) and the resulting spheroids are dried, sifted, and optionally blended prior to storage.

Optionally, an initial seal coat can be applied to the uncoated multiparticulates. For example, an initial seal coat composed of HPMC and purified water can be applied on a fluid bed coater, e.g., by spraying.

The enteric coat can be applied directly to the uncoated spheroid core, i.e., the uncoated multiparticulate, or may be applied over an initial seal coat. The enteric coat as described above, is typically applied on a fluid bed coater.

In one embodiment, a final seal coat is applied over the enteric coat and, optionally, talc is utilized as a final step prior to filling the multiparticulates into a suitable packaging unit.

## III. Formulations/Kits/Methods of delivery

In another embodiment, the present invention provides products containing the pantoprazole multiparticulates of the invention.

In one embodiment, the pantoprazole microparticulates are packaged for use by the patient or his caregiver. For example, the microparticulates can be packaged in a foil

or other suitable package and is suitable for mixing into a food product (e.g., applesauce or the like) or into a drink for consumption by the patient.

In another embodiment, the pantoprazole microparticulates are suspended in a physiologically compatible suspending liquid.

In yet another embodiment, the pantoprazole microparticulates are filled in capsules, caplets or the like for oral delivery.

In still a further embodiment, the invention provides method of treating a subject in need thereof by administering an effective dose of the pantoprazole microparticles of the invention.

The following examples illustrate specific embodiments of the invention and are not a limitation on the present invention.

## Example 1 – Batch A

Using a NICA extruder/spheronizer, during initial formulation development, several prototypes of uncoated multiparticulates were manufactured to obtain a target immediate release profile similar to or faster than the pantoprazole sodium uncoated tables, currently available as Protonix (20 mg and 40 mg) tablets. Levels of the disintegrant crospovidone from 5 to 28.5% and the binder hydroxypropyl methyl cellulose (HPMC 2280) from 0.5 to 1% were evaluated during preparation of uncoated multiparticulates over four batches.

A. *Preparation of Uncoated Pantoprazole Sodium Multiparticulates*

More particularly, pantoprazole sodium sequihydrate, microcrystalline cellulose, PHMC K3 and sodium carbonate are dry blended in a Hobart mixer. Thereafter, polysorbate 80, NF (vegetable source) and purified water, USP, are added to the Hobart mixer. The resulting granulated produce is extruded and spheronized in a Nice extruder/spheronizer and the spheroids are tray dried and sifted, following by transfer to a PK blender. The final spheroids are stored in drums.

One of the batches (an approximately 200 gm batch) with 15% disintegrant crospovidone and with 1% HPMC 2280 was selected as a prototype with

similar release profile. The sieve cut of the uncoated spheroids from this batch was between 500 – 1000 microns.

B. *Prototype Lab Batch*

Approximately 100 grams of these uncoated spheroids were coated in a 3" Wurster Fluid Bed coater with HPMC, Eudragit L30D55 and HPMC to result in Enteric coated multiparticulates.

The % w/w of the dry polymer Eudragit L30D-55 used was 22.16%. In the coating batch, talc was introduced as dry powder in the coating chamber instead of being a part of the suspension. This was due to the small nozzle size (0.5 mm) used for coating the 100 g batch, which could potentially be clogged. The percent of talc and triethyl citrate used for the lab batch was less as compared to the clinical batches which were subsequently prepared. The multiparticulates were hand filled into size #2 HPMC capsules at a fill weight of 206 mg. The capsules were tested in vitro in 0.1 N Hcl and pH 6.8 phosphate buffer. Less than 1% was released in acid media and greater than 80% was released in basic media as desired.

These capsules were tested in dogs. The $C_{max}$ and AUC were compared against the current marketed Protonix 20 mg tables (and values were extrapolated to the 40 mg strength). It was seen that these multiparticulates released drug at a much faster rate than the current Protonix tablet in pH 6.8 phosphate buffer as desired. The final seal coat comprises hydroxypropyl microcellulose (HPMC) and water. This batch was packaged as spheroids in clear glass vials and placed on stability at accelerated conditions (30 °C/60% relative humidity (RH) and 40 °C/75% RH). The stability was monitored for 3 months. The capsules filled with multiparticulates equivalent to 40 mg strength were stable over the three month period and met all dissolution and stability criteria.

Dissolution was tested by filling the stored spheroids into capsule shells, and dissolving in 0.1 N HCl (target release at 2 hours: not more than (NMT) 10%), followed by dissolution in phosphate buffer (target release at 45 min: not less than (NLT) 75%. The acceptance criteria further required a strength of 90 to 100% of the label claim.

Table 1

| Test | Time | Strength (HPLC) % Label | Dissolution – Percentage Released (avg) | |
|---|---|---|---|---|
| Unit | | | 0.1 N HCl | Secondary dissolution in phosphate buffer |
| Initial | | 100.0% | 0.9% | 91.6% |
| Ambient Room Temp | 1 month | 97.2% | 0.8% | 88.5% |
| | 7 month | 108.5% | 0.8% | 94.1% |
| 30 °C/60% RH | 1 month | 99.3% | 0.5% | 83.4% |
| | 2 month | 98.3% | NA | NA |
| | 3 month | 104.4% | 0.7% | 82.2% |
| 40 °C/75% RH | 1 month | 95.4% | 0.7% | 86.1[1] |
| | 2 month | 97.3% | NA | NA |
| | 3 month | 102.7% | 0.7% | 89.4% |

[1] One capsule – 78% released.

## Example 2 – Batch B

Based upon the lab batch A, a further scale-up batch of 1400 g was manufactured using a 7" wurster fluid bed coater. During coating for this batch, the level of HPMC initial seal coat was 2% of the weight of the uncoated multiparticulates as compared to 4% for the coated batch A. The % w/w of the dry polymer, Eudragit L30D-55 used was 22.16% w/w. Also, the talc was added directly to the coating suspension as a larger nozzle size (1 mm) was used.

Initial release of coated microparticulates in 0.1 N acid was high (9.0%) and very close to the limit of 10%. This Batch (B) did not meet the stability and dissolution criteria when tested at accelerated conditions (30 °C/60% relative humidity (RH) and 40 °C/75% RH). Trial from this batch indicated that an initial seal coat of greater than 2% of uncoated microparticulates enhances stability of the multiparticulates. Additionally, more enteric polymer loading may be beneficial to control the release in acid media as the process is scaled up.

## Example 3 – Scale-Up Batch

A. *Technical Batch*

Using a NICA extruder/spheronizer, a 36 kg technical batch of multiparticulates was prepared and 20 kg were enteric coated in a Glatt GPCG-15 to

result in a 32 kg batch of multiparticulates. The % w/w of the dry polymer, Eudragit L30D55 used was 22.16% w/w. This batch was filled into size #3 HPMC capsules at a fill weight of 156 mg. the release in 0.1 N HCl at 2 hours was greater than the desired 10%. Based on this, taking into account scale-up effects, minor adjustments were made the formula and process for clinical batch.

B. *Clinical Batch*

Two 12 kg sub batches of a wet granulated mass were extruded and spheronized on a NICA extruder/spheronizer resulting in wet multiparticulates. The multiparticulates were tray dried at 40 °C for 10 to 12 hours to the desired % LOD of 3.4% to 4.3%. The batch size of uncoated microparticulates was reduced to 16 kg to ensure uniformity and completeness of coating. 16 kg of the dried, sieved uncoated multiparticulates were coated with an initial HPMC seal coat, followed by an Eudragit L30D55 enteric coat, followed by an HPMC final coat to result in 33 kg of coated multiparticulates. This batch was filled into size #2 HPMC capsules at a fill weight of 206 mg.

The release in 0.1 N HCl at 2 hours was less than the 10% limit and in pH 6.8 phosphate buffer, it was greater than the 80% limit. The batch met in vitro release characteristics. The one month stability date showed that the multiparticulates were stable at 40 °C/75% RH for one month. The spheroid filled capsule had a faster in vitro release (dissolution) as compared to the Protonix 40 mg table in pH 6.8 phosphate buffer.

## Example 4 – Evaluation of Batch A Formulation in Beagle Dogs

The in-vitro release data of the sodium pantoprazole multi particulate formulation shows a faster release than the current marketed tablet. This provides earlier absorption and thereby a faster onset of action. The dog data clearly shows earlier drug levels of sodium pantoprazole from multiparticulates as compared to the single monolithic tablets. Earlier onset of action provides faster relief from gastric pain and other GI disorders.

Pantoprazole Mg and Pantoprazole Na Formulations have been evaluated in Beagle Dogs (n=5). The mean (SD) pharmacokinetic parameters and relative bioavailability of pantoprazole is illustrated in the table below.

As illustrated, the non-optimized lab batch of sodium pantoprazole multiparticulate formulation dosed in dogs shows smaller lag time than the current marketed tablet.

| Parameter | 20mg Market Tablet Batch A98D015 Pantoprazole Na[a] | 40mg Multiparticulate Capsule Batch A with enteric coat - Pantoprazole Na |
|---|---|---|
| AUC (μg*hr/mL) | 16.3 (2.46) | 17.3 (2.33) |
| Cmax (μg/mL) | 11.7 (3.55) | 7.10 (1.76) |
| tmax (hr) | 1.70 (0.84) | 1.20 (0.27) |
| tlag (hr) | 1.10 (0.91) | 0.25 (0.18) |
| t ½ (hr) | 0.62 (0.17) | 0.77 (0.21) |
| Relative Bioavailability | -- | AUC: 106%[b]<br>Cmax: 61%[b] |

a: AUC and Cmax normalized to a 40mg dose
b: Relative to Market Product Tablet

The dog data of the sodium pantoprazole multi particulate formulation gives a similar AUC as the current marketed tablet. Without wishing to be bound by theory, it is believed that the faster release and similar AUC of the multi particulates is achieved by lowering the level of the disintegrating agent crospovidone (as compared to the level in the tablet) and incorporating the functional excipient polysorbate 80 in the core of the spheroids.

All documents identified herein are incorporated by reference. One of skill in the art will recognize that minor modifications to the conditions and techniques described in the specific embodiments described herein can be varied without departing from the present invention. Such minor modification and variants are within the scope of the invention as defined by the following claims.

Claims:

1. Pantoprazole microparticles having reduced release under gastric conditions and fast release at neutral pH, wherein each of said microparticles comprises:

a spheroid core comprising pantoprazole or an enantiomer thereof, or a salt thereof, and a surfactant;

an enteric coat on the core, said enteric coat in the range of about 15 to 45 % w/w of the microparticle and comprising a copolymer of methacrylic acid and methacrylates; and

wherein said microparticles have an average size no greater than about 1mm in diameter.

2. The pantoprazole microparticles according to claim 1, further comprising a final seal coat on the enteric coat.

3. The pantoprazole microparticles according to claim 2, wherein the final seal coat comprises about 1 wt% of the microparticle.

4. The pantoprazole microparticles according to claim 1, wherein the surfactant is a polysorbate.

5. The pantoprazole microparticles according to claim 1, wherein the polysorbate is polysorbate 80.

6. The pantoprazole microparticles according to claim 1, wherein the final seal coat comprises hydroxypropyl microcellulose (HPMC) and water.

7. The pantoprazole microparticles according to claim 1, wherein the enteric coat comprises 27.5 to 32. 5 % w/w of the microparticle.

8. The pantoprazole microparticles according to claim 1, wherein the enteric coating comprises about 30% w/w of a 30 wt% dispersion of Eudragit L 30 D55 coating; about 15% w/w talc, about 3% triethyl citrate; a pH adjuster and water.

9. The pantoprazole microparticles according to claim 1, further comprising 40 mg pantoprazole per 100 mg microparticle.

10. The pantoprazole microparticles according to claim 1, wherein said spheroid core further comprises a binder, a pH adjuster and hypromellose.

11. The pantoprazole microparticles according to claim 10, wherein the binder is selected from the group consisting of microcrystalline cellulose and crospovidone, and mixtures thereof.

12. The pantoprazole microparticles according to claim 1, wherein the spheroid core consists essentially of:

| | |
|---|---|
| pantoprazole sodium sesquihydrate | 45.24% w/w |
| microcrystalline cellulose | 27.25% w/w |
| polysorbate 80 | 5 % w/w |
| crospovidone | 15 % w/w |
| hypromellose 2208 | 1 % w/w |
| sodium carbonate | 6.5% w/w |
| purified water | q.s. |

13. The pantoprazole microparticulates according to claim 1, further comprising an initial seal coat between the core and the enteric coat.

14. A pantoprazole formulation for use in dosing to pediatric patients, said formulation comprising a suspension comprising the pantoprazole microparticles of Claim 1 and a physiologically compatible suspending liquid.

15. A capsule comprising the pantoprazole microparticles of claim 1.

16. A foil packet comprising the pantoprazole microparticles of claim 1.

17. A method of treating humans in need of pantoprazole, said method comprising the step of administering an effective dose of the pantoprazole microparticles of claim 1.

18. A method of producing a multiparticle formulation of pantoprazole, said method comprising the steps of:

producing a spheroid core comprising pantoprazole or an entantiomer thereof, or a salt thereof, and a surfactant via extrusion and spheronization;

applying an enteric coating to the spheroid core, said enteric coating comprising a copolymer of methacrylic acid and methacrylates in an amount that provides the microparticle with 15 to 45 % w/w enteric coating; and

optionally applying a final seal coat to the enteric-coated spheroid core, said final seal coat being about 1 wt% of the microparticle;

wherein said microparticles have an average size of no greater than about 1mm in diameter.

19. The method according to claim 1, further comprising the step of applying an initial seal coat to the spheroid coat prior to applying the enteric coating.

20. The method according to claim 1, wherein the enteric coating is sprayed as a suspension onto the spheroid core.

## ABSTRACT OF THE DISCLOSURE

Pantoprazole sodium multiparticulates are described which avoid sticking to nasogastric and gastronomy tubes. The pantoprazole microparticles have a spheroid core of pantoprazole or an enantiomer thereof, or a salt thereof, and a surfactant; an enteric coat on the core, and a final seal coat over the enteric coat, which is composed of hydroxypropyl microcellulose (HPMC) and water.

# Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US04/033058

International filing date: 30 September 2004 (30.09.2004)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/507,810
Filing date: 01 October 2003 (01.10.2003)

Date of receipt at the International Bureau: 19 November 2004 (19.11.2004)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse